Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. *Krupitsky E, Nunes EV, Ling W, et al. Lancet 2011; 377:1506-13*

Concerns about injectable naltrexone for opioid dependence. *Wolfe D, Carrieri MP, Dasgupta N, et al. Lancet 2011; 377:1468-69*

This is a randomised trial where patients who had 30 days or less of inpatient detoxification and 7 days or more off all opioids were enrolled at 13 clinical sites in Russia. Participants received either 380mg of extended-release injectable naltrexone (XR-NTX) or placebo. All participants received 12 biweekly counselling sessions. The primary endpoint was confirmed abstinence during weeks 5 to 24. They also looked at secondary endpoints including: opioid-free days, opioid craving scores and number of days of retention.

Overall 250 people were assigned to either XR-NTX (n=126) or placebo (n=124). In total 67 of the XR-NTX group (53%) and 47 of the placebo group (38%) completed the trial. The results showed that patients in the XR-NTX group self-reported a median of 99.2% opioid-free days compared with 60.4% for the placebo group. There was a significant reduction in craving and median retention was 168 days in the XR-NTX group compared with 96 days in the placebo group.

SMMGP comment: In the last Clinical Update we reported on a Cochrane review that found there is a lack of any absolute evidence for the efficacy of oral naltrexone. So - is the injectable formulation any better?

This study shows that injectable naltrexone has some efficacy. However, there are limitations. One of the greatest risks identified with oral naltrexone is the risk around overdose. This study doesn't fully address this and concern around safety must remain – particularly when only 53% completed the trial to 24 weeks.
The accompanying commentary highlights some ethical issues around this study. Using a placebo-control is usually not considered appropriate when an accepted standard of treatment exists. In Russia this is indeed the case – it being one of the 122 of 192 UN member states that don't offer opiate substitution therapy. This is a significant and serious limitation when interpreting this study. Overall the study suggests that injectable naltrexone shows distinct promise but a wholesale adoption without crucial overdose data would be premature. It is important that its use is fully evaluated in a comprehensive treatment system based on patient choice rather than an ethically dubious climate of state enforced abstinence.

Outcomes of treatment for hepatitis C infection by primary care providers. *Arora S, Thornton K, Murata G, et al. NEJM 2011;364;2199-2207.*

This was a prospective cohort study comparing treatment for hepatitis C infection (HCV) at the University of Mexico HCV clinic with treatment by primary care clinicians at 21 sites in rural areas and prisons in New Mexico. These sites were all part of the Extension for Community Healthcare Outcomes (ECHO) model which was developed to improve access to underserved populations with complex health problems. They use video-conferencing techniques to train primary care providers to treat complex diseases.

A total of 407 patients with chronic HCV infection were enrolled for treatment. The primary end point was sustained virological response (SVR). At the university clinic they treated 146 patients and achieved SVR in 84 (57.5%) and there was no significant difference at the ECHO sites where they treated 261 patients and achieved SVR in 152 (58.2%). They achieved around the same rates of SVR in those with genotype 1. Serious adverse

events occurred in 13.7% of patients at the university clinic and 6.9% of the patients at ECHO sites.

Factors associated with hepatitis C knowledge among a sample of treatment naïve people who inject drugs. *Treloar C, Hull P, Joanne Bryant, et al. Drug and Alcohol Dependence 2011;116:52-56*

This was a cross-sectional study designed to evaluate treatment considerations in people with self-reported hepatitis C infection in New South Wales, Australia. Participants were recruited from needle exchanges, opiate substitution clinics, pharmacies dispensing opiate substitution and from the mailing list of a community-based hepatitis C organisation. They then completed a self-administered survey which had 48 items and assessed knowledge around the natural history and treatment of hepatitis C.

Overall, knowledge of hepatitis C natural history, treatment and ineligibility criteria was poor. The knowledge of side effects and factors influencing treatment success was moderate but 25% of participants scored zero on these items. Knowledge was low in most domains and the impact of hepatitis C on health was over-estimated. This is despite the reported finding that half of the sample had asked a healthcare worker for more information on treatment and a quarter had seen a specialist.

SMMGP comment: One has to be careful here not to overinterpret the first study. The healthcare system in New Mexico differs significantly from the UK but the crucial element is that secondary care and specialist support remain critical to the delivery of HCV treatment. The study is not a mandate for primary care to launch out on their own but to recognise that models of care where care is delivered physically close to the patient are crucially important. This is particularly so when delivering HCV treatment to a population that is predominantly injecting drug users – an issue not addressed in New Mexico.
The second study highlights that knowledge around hepatitis C for individuals and clinicians remains crucial and needs to be developed. The new *RCGP Part 1 Certificate in the detection, diagnosis and management of hepatitis B and C* is being rolled out this year. The emodule is available now, free to all (on registration) http://elearning.rcgp.org.uk A cohort of trainers is being trained and this should mean that national and local training days will be available in the autumn across the country. Contact Marianne at the RCGP on hepbandc@rcgp.org.uk if you want more details on future Part 1 training day events.

Slow-release oral morphine for opioid maintenance: a systematic review. *Jegu J, Gallini A, Soler P, et al. British Journal of Clinical Pharmacology 2011; 71:832-843*

This review summarises the results of all available clinical trials looking at the use of slow-release oral morphine (SROM) for opioid maintenance treatment. In total they identified 13 articles that reported on nine clinical trials. They looked at the outcomes for retention rate, quality of life, withdrawal symptoms, craving, additional drug consumption and adverse events. Of these nine studies only one was a randomised trial and one had controls but no randomisation. The other seven studies had no control group.

Retention rates in studies varied from 95% at 6 months to 81% at 4 weeks but only a single study compared SROM to methadone (84.4% at 7 weeks with SROM *vs.* 90.6% with methadone). In addition, this study found that quality of life scores were not significantly different.

In almost all the uncontrolled studies the outcomes for quality of life, withdrawal symptoms, craving and additional drug use were improved with SROM maintenance. The only randomised controlled trial was an Austrian study which used a 7 week crossover design. It recruited 32 individuals and the results showed improvements across the board but few significant differences between the groups. Patients in this study receiving SROM had significantly lower depression, anxiety and fewer physical complaints.

SMMGP comment: Methadone and buprenorphine enjoy an almost complete hegemony when it comes to opioid maintenance. However, there is simply insufficient evidence at present to suggest that slow release oral morphine is equivalent to methadone.

The Orange Book gives SROM a brief paragraph suggesting that it could be useful in those who aren't 'held' on methadone or don't tolerate it. The RCGP/SMMGP opioid guidance (available at http://www.smmgp.org.uk) expands a little more. It highlights the use of SROM in Europe and cites the Austrian paper that suggested equivalent outcomes to methadone with some evidence suggesting it improved well-being. This is the single randomised controlled trial referred to in this review but the crossover design used is arguably a flawed one.

Misuse remains a concern and the authors report on a recent study suggesting that the number of deaths related to morphine may have increased after the introduction of SROM in parts of Austria. So, for the moment, SROM for opioid maintenance has a very limited evidence base and remains a specialist option which most in primary care won't be considering.

The pharmacodynamics and pharmacokinetic profile of intranasal crushed buprenorphine and buprenorphine/naloxone tablets in opioid abusers. *Middleton LS, Nuzzo PA, Lofwall MR, et al. Addiction 2011. Available online ahead of print.*

This was a study conducted in an in-patient research unit in the USA. They took 10 healthy adults who were abusing, but not dependent on, intranasal opioids. It was a 3½ week in-patient study and it was a randomised, double-blind, within-subject placebo-controlled design. The individuals received six sessions of the drugs – in five of them they were given intranasal doses and one where they given an intravenous dose of buprenorphine/naloxone. The experimenters took plasma samples, physiological, subject- and observer-rated measures before and for up to 72 hours after administration.

Overall, both preparations were safely tolerated and produced subjective and physiological *mu* opioid effects. The results did show higher subjective ratings and street values for buprenorphine versus buprenorphine-naloxone but they weren't statistically significant. Intranasal administration was shown to work faster. In this study the onset of the drug action was within 15 minutes and peak response was at 60-75 minutes. (Sublingual buprenorphine usually works within 30-45 minutes and peaks at 2-3 hours.) Normal bioavailability via the sublingual route can be as low as 15%. In this study the bioavailability of crushed buprenorphine taken intranasally ranged between 38 and 44%. Naloxone did not alter these effects.

Naloxone was absorbed readily after intranasal buprenorphine/naloxone with an estimated bioavailability of between 24 and 30%.

SMMGP comment: Clinical experience tells us that the snorting of buprenorphine and buprenorphine/naloxone is a major problem related to diversion and misuse of these drugs. In prison it is commonly reported that a single 8mg buprenorphine tablet is divided into multiple doses to snort. This study shows that snorting buprenorphine means the user gets more drug and gets it quicker. Potentially the bioavailability of buprenorphine is 2 to 3 times greater when snorted and that fits with the reports of people still getting effects when they snort relatively small amounts.

The effect of adding naloxone to the mix is less clear. The naloxone had no effect on the action of the buprenorphine. The bioavailability of naloxone in this study suggests that it could be sufficiently great to precipitate acute withdrawal in opioid-dependent individuals but it hasn't been reported in the literature.

Severity of alcohol problems and readiness to change alcohol use in primary care. *Krenek M, Maisto SA, Funderburk JS, Drayer R. Addictive Behaviors 2011;36:512-515*

This was a short paper that looked at the clinical utility of the Alcohol Use Disorders Identification

Test (AUDIT) and its abbreviated version AUDIT-Consumption (AUDIT-C). Specifically, it wanted to know how useful it was as a predictor of readiness to change alcohol use in a primary care setting. They took 114 participants who completed the full AUDIT questionnaire, the readiness to change ruler and an alcohol use disorders diagnostic interview. They also had two AUDIT-C measurements – one derived from the AUDIT questionnaire and another undertaken during a primary care visit.

The results showed that the AUDIT and the number of dependence symptoms significantly predicted readiness to change independently of other variables. The study did not provide evidence that AUDIT-C is useful in predicting a patients' readiness to change. Additionally, there was a poor correlation between the two AUDIT-C scores even though these were done within a relatively short period of time.

SMMGP comment: The AUDIT questionnaire is firmly embedded in the NICE recommendations for the assessment of alcohol problems in primary care. With practice it is quick and easy to do and, importantly, it identifies those who would benefit from a brief intervention.

The authors speculated that the poor correlation of AUDIT-C results may have been as a consequence of one being done as a paper-based exercise and the other in primary care could be either paper or an interview format. AUDIT and AUDIT-C questionnaires were originally designed to be paper or computer administered questionnaires. However, this paper helps to underline the usefulness of AUDIT in the management of alcohol problems in primary care. Not only does it identify patients drinking at hazardous levels but it will also provide an indication of the patients' readiness to change.

Determining the efficacy of auricular acupuncture for reducing anxiety in patients withdrawing from psychoactive drugs. *Black S, Carey E, Webber A. Journal of Substance Abuse Treatment 2011. Available online ahead of print.*
This study used a randomised controlled design with a sample of 101 patients recruited from an addiction treatment service in Canada. The subjects were allocated to one of three treatment groups. The first group received auricular acupuncture as per the National Acupuncture Detoxification Association (NADA). There were two control groups: one using auricular acupuncture at sham points and the other a treatment setting (relaxation) control group. These interventions were given over three treatment sessions. The primary outcome was the effect of treatment on subject state anxiety – this was measured using the Spielberger State-Trait Anxiety Inventory (STAI) before and after treatment. Secondary outcomes included changes in heart rate and blood pressure evaluated before and after treatment.
The results showed that there was no difference between the acupuncture, sham acupuncture or relaxation control group.

SMMGP comment: This was a well-designed study with objective outcomes measures. It had sufficient statistical power, it had a sham control group and a relaxation control group with no acupuncture. It found that the intervention made no difference. According to the authors auricular acupuncture is used in more than 700 treatment centres worldwide. Many organisations will probably continue to offer auricular acupuncture as part of their service. This study offers strong evidence that there is no effect.

Managing borderline personality disorder and substance use. An integrated approach. *Lubman DI, Hall K, Pennay A, Rao S. Australian Family Physician 2011;40;376-38. Available at http://www.racgp.org.au/afp*

This practical review aims to provide an overview of how the general practitioner can provide effective support for patients with borderline personality disorder (BPD) and substance use disorders (SUD). The article highlights that population surveys have suggested that 1-2% of the general population have BPD. In primary care it has been suggested it could be around four times this prevalence and some studies have reported that up to 65% of substance users meet the criteria for BPD.

The article raises some key points. It notes that treatment outcomes are poorer and there is a greater risk of harm for people with a diagnosis of comorbid BPD and SUD. The article then goes on to highlight the central role that a positive therapeutic relationship plays. The authors suggest that an 'explanatory framework' for challenging behaviours, mechanisms for reflective countertransference, and skills to respond adequately to behaviours which jeopardise treatment retention are recommended. It also suggests that opioids or benzodiazepines should be prescribed with caution. They go on to make suggestions around longterm psychotherapy, crisis management, treatment contracting, collegial support and clinical supervision.

SMMGP comment: This is not a deeply systematic mechanistic review but a practical article that suggests some practical measures to help manage people in this difficult combination. Some of the suggestions to manage BPD and SUD are pragmatic and achievable. The management of chronic suicidality in patients with BPD and SUD is a helpful guide and the risk of burnout in treating practitioners is highlighted. However, some of the suggestions are less useful - for instance, it is difficult to envisage a situation in UK practice where referral for longer term psychotherapy with a psychiatrist or clinical psychologist will be an easily accessible option.

Acute effects of waterpipe tobacco smoking: a double-blind, placebo-control study. *Blank MD, Cobb CO, Kilgalen B, et al. Drug and Alcohol Dependence 2011;116;102-109*

This paper claims to be the first randomised controlled study that compared the physiological and subjective effects of waterpipe tobacco smoking. They took 37 occasional (2-5 monthly smoking episodes for ≥6 months) waterpipe tobacco smokers and they completed two double-blind smoking sessions. They smoked either their preferred brand of waterpipe tobacco or a flavour-matched tobacco-free preparation. They measured blood and expired carbon monoxide, cardiovascular and respiratory responses. They also assessed the subjective responses in the participants to each of the sessions.

Smoking tobacco with a waterpipe resulted in significant increases in plasma nicotine, heart rate and evidence of substantial carbon monoxide exposure. When smoking the non-tobacco products there was no rise in either plasma nicotine or heart rate but there was a similar exposure to carbon monoxide. The results suggest clearly that the rise in heart rate is due to tobacco-delivered nicotine and not the carbon monoxide exposure. They also showed that FEV1 and FVC significantly decreased from pre- to post-smoking. It was noted that the subjective effects were not related to the exposure to nicotine.

SMMGP comment: One of the attractions of water pipes is that they are perceived to be safer – a way of taking tobacco, cannabis or other substances without the risk of 'normal' smoking. There is already some good evidence that waterpipes can cause issues with lung disease, cardiovascular disease and dependence. This study was particularly interested in the acute effects rather than the issues of long-term damage. Waterpipes use charcoal as the heat source and this is the source of carbon monoxide and known carcinogens. The delivery of similar amounts of carbon monoxide reinforces the message that waterpipe smoking of non-tobacco products still carries health risks.

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